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Serious hematologic reactions associated with ticlopidine — update

Ticlopidine hydrochloride is a thienopyridine derivative that inhibits platelet aggregation irreversibly by inhibiting adenosine-diphosphate-induced platelet-fibrinogen binding.<1,2> It was first approved for sale in Canada in 1991 and is indicated for the "reduction of the risk of first or recurrent stroke for patients who have experienced at least one of the following events: complete thromboembolic stroke, minor stroke, reversible ischemic neurological deficit, or transient ischemic attack including transient monocular blindness."<1> Other uses not listed in the product monograph are to reduce the risk of myocardial infarction in patients with unstable angina,<3> to improve patency in vein bypass grafts used to treat peripheral vascular disease,<4> to treat intermittent claudication and, in combination with ASA, to prevent thrombus formation after coronary artery stenting.<2>

Ticlopidine has been associated with serious or fatal adverse drug reactions including thrombotic thrombocytopenic purpura (TTP),<5,6> thrombocytopenia,<7> bone marrow aplasia,<8,9> anemia,<8,9> pancytopenia,<8-10> agranulocytosis<6,7> and neutropenia.<7> Recent reports have drawn attention to the increased risk of TTP associated with the use of ticlopidine after coronary artery stenting.<2,6> A recent retrospective study involving 43 322 patients who underwent stenting revealed 1 case of TTP per 4814 patients (0.02%).<2>

Between July 1991 and June 1999 the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) received 464 reports of adverse reactions associated with the use of ticlopidine. Of these, 138 concerned adverse reactions of a hematologic nature (Table 1).

The CADRMP also looked at reports in which ticlopidine had been used in patients who had undergone coronary angioplasty alone or with stent insertion (Table 2). Thirteen of the 32 reports found were of platelet, bleeding or clotting disorders, and 4 were of granulocytopenia or agranulocytosis, for a total of 17 reports of serious or fatal hematologic reactions.

The number of serious and fatal adverse reactions evident from the CADRMP reports is consistent with what is known about the risks associated with ticlopidine. Hematologic monitoring of the leukocyte count along with a differential and a platelet count is recommended at baseline and every 2 weeks until the end of therapy. If therapy has been discontinued, an additional complete blood count with differential should be done 2 weeks after the discontinuation of therapy because of the long half-life of ticlopidine (terminal elimination half-life 4-5 days).<1> However, hematologic reactions have been reported to occur within 1 week of beginning ticlopidine therapy and up to 19 days after the completion of therapy.<2,5> Steinhubl and associates<2> have questioned whether routine monitoring of blood counts is likely to "unmask TTP prior to clinical presentation." It is therefore recommended that patients be counselled about early warning signs of hematologic problems including signs of infection, bleeding or neurologic deficit.<2,7>

Table 1: Hematologic adverse reactions associated with ticlopidine use reported to the CADRMP between July 1991 and June 1999

Adverse reaction	No. of reports* (and no. of deaths)
Granulocytopenia, leukopenia or agranulocytosis	72 (3)
Pancytopenia (or pancytopenic picture†)	15 (6)
Thrombotic thrombocytopenic purpura	7
Disseminated intravascular coagulation	1 (1)
Thrombocytopenic purpura	1
Thrombocytopenia	12 (2)
Thrombocytopenia with granulocytopenia	5
Thrombocytopenia with anemia	3
Granulocytopenia with anemia	5
Anemia	6
Bleeding with or without anemia	9 (3)‡
Lymphopenia	2
Total	138 (15)

Note: CADRMP = Canadian Adverse Drug Reaction Monitoring Program.
*Each report is included in only one adverse reaction category.
†Thrombocytopenia, granulocytopenia/leukopenia and anemia.
‡One death was unrelated to drug administration; another was associated with hepatorenal syndrome and hepatic necrosis.

Table 2: Summary of adverse reactions in patients receiving ticlopidine who had undergone either coronary angioplasty or coronary angioplasty with stent insertion

	Procedure; no. of reports		
Adverse reaction	Angioplasty	Angioplasty with stent insertion	Total
Thrombotic thrombocytopenic purpura	1	2	3
Thrombocytopenia	1	7	8
Hemorrhage		2	2
Granulocytopenia	1	2	3
Agranulocytosis		1	1
Other*	6	9	15
Total	9	23	32

*Includes reports that do not contain hematologic reactions.

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Leukotriene receptor antagonists: suspected adverse reactions

The cysteinyl leukotrienes are inflammatory mediators that bind to cysteinyl leukotriene receptors found in the human airway and cause a number of airway actions including bronchoconstriction, mucous secretion, vascular permeability and eosinophil recruitment.<1> Zafirlukast (Accolate®) and montelukast sodium (Singulair®), marketed in Canada since November 1997 and August 1998 respectively, are competitive cysteinyl leukotriene receptor antagonists. Zafirlukast is indicated for the prophylaxis and chronic treatment of asthma in patients 12 years of age and older.<2> Montelukast is indicated for the prophylaxis and chronic treatment of asthma, the treatment of asthma in ASA-sensitive patients and the prevention of exercise-induced bronchoconstriction in pediatric patients 6-14 years of age and adults 15 years of age and older.<1>

As of June 1, 1999, the CADRMP has received 41 reports of suspected adverse drug reactions associated with the use of zafirlukast and 22 associated with the use of montelukast. This article will discuss a serious and rare adverse reaction associated with the use of these agents, drug-drug interactions and unexpected adverse reactions that have been reported to the CADRMP.

Eosinophilic conditions

Rare cases of eosinophilic conditions have occurred during the use of these medications.<1,2> These adverse reactions have been reported as eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications and/or neuropathy, sometimes presenting as Churg-Strauss syndrome, a systemic eosinophilic vasculitis.<2> It is unclear whether these adverse events are related to the use of the leukotriene receptor antagonists or if the clinical syndrome is unmasked with the reduction or withdrawal of systemic steroids.<3> The eosinophilic syndrome has occurred in steroid-dependent asthmatic patients who did not use zafirlukast when their steroid dose was decreased or eliminated.<4> This syndrome has also occurred in asthmatic patients receiving zafirlukast following corticosteroid treatment withdrawal.<5> Others have reported Churg-Strauss syndrome with zafirlukast therapy in patients not receiving systemic steroid treatment.<6,7> Although the exact causes of this rare syndrome remain unclear, physicians should be aware of the possibility of vasculitis and eosinophilic conditions presenting in these circumstances.

The CADRMP has received 5 cases in which the terms "vasculitis" or "vasculitis allergic" were reported in conjunction with other reactions. Four cases were associated with the use of zafirlukast alone, and in 1 case both zafirlukast and montelukast were listed as suspect drugs but the patient was taking montelukast at the time of the adverse reaction. The diagnosis reported with each of these 5 cases was: Churg-Strauss disease, possible Churg-Strauss syndrome, hypereosinophilia syndrome/vasculitis, drug-induced leukocytoclastic type vasculitis (Churg-Strauss syndrome and asthma documented in history) and allergic polyarthritis/vasculitis. Eosinophilia was also reported in the first 3 cases.

Eosinophilia was reported without vasculitis in 1 case. A 66-year-old woman receiving zafirlukast for chronic obstructive pulmonary disease developed eosinophilia (eosinophil count 1280 × 10^6/L, normally 50-250 × 10^6/L) along with myocardial infarction, chest pain, ST-segment elevation, pericarditis, pruritus and maculopapular rash.

Drug-drug interactions

Because both montelukast and zafirlukast are metabolized by the cytochrome P450 enzyme system, there is a theoretical potential for drug interactions with numerous agents. Montelukast is metabolized by cytochrome P450 3A4 and 2C9.<1> In drug-interaction studies, the recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following drugs: theophylline, prednisone, prednisolone, oral contraceptives (ethinyl estradiol/norethindrone 35/1), terfenadine, digoxin and warfarin.<1> Zafirlukast is metabolized by cytochrome P450 2C9 and inhibits P450 3A4 and 2C9 at serum concentrations close to clinically achieved plasma concentrations.<2> Concomitant administration of warfarin with zafirlukast produces clinically significant increases in prothrombin time.<2> Erythromycin, ASA, theophylline and terfenadine are reported to affect zafirlukast concentrations.<2> The product monograph states that "theophylline may result in decreased plasma levels of zafirlukast, without effect on plasma theophylline levels"; however, there is at least one published case of a serious drug-drug interaction between zafirlukast and theophylline in which serum theophylline levels increased to the toxic range shortly after the addition of zafirlukast to the regimen.<8> This drug-drug interaction reappeared when the 2 medications were rechallenged after interruption of treatment. The authors suggested that a sufficiently high serum concentration of zafirlukast was achieved in this patient to inhibit cytochrome P450 1A2, which metobolizes theophylline along with P450 2E1.<8>

The CADRMP has received 2 reports of drug interactions associated with the use of zafirlukast. The first case involved a 40-year-old woman who had been taking carbamazepine for many years (history of cerebral palsy, hypertension and asthma). About a week after starting zafirlukast therapy (20 mg twice daily), the patient's carbamazepine level "doubled." Therapy with diltiazem, which may also increase carbamazepine serum levels, had been started 6 weeks before the zafirlukast without evidence of adverse reaction. The event resolved after zafirlukast was discontinued, and the carbamazepine dose was held until the carbamazepine level returned to normal.

The second case is complex because it involved 3 suspect drugs – cisapride, nefazodone and zafirlukast – and numerous concomitant medications, including theophylline. The 37-year-old woman with a history of asthma, depression, gastroesophageal reflux disease and hypertension was in hospital following surgery for fundoplication. She died after receiving 4 doses of cisapride (20 mg twice daily). The patient had no history of cardiac problems, and the theophylline level (10 mg/L) was within the therapeutic range (10-20 mg/L). Blood levels of cisapride were 170 ng/mL at autopsy. The Prepulsid® product monograph states that a cisapride dose of 10 mg 3 times daily produces steady-state plasma levels between 20 and 40 ng/mL before the morning dose and evening peak levels between 50 and 100 ng/mL. Nefazodone and zafirlukast are both known to inhibit cytochrome P450 3A4 enzyme, by which cisapride is mainly metabolized.

Other unexpected adverse reactions

- Tachycardia associated with the use of montelukast was reported in 5 patients. In 4, tachycardia was the only reported adverse reaction; these patients were 8, 9 and 13 years of age (age not reported in 1 case). In the fifth report tachycardia along with vomiting, chills, headache, hyperglycemia and hypertension occurred suddenly in a 26-year-old patient 2 hours after the first dose of montelukast. This patient had a history of uncontrolled asthma (treated with Theo-Dur®, Pulmicort® and ipratropium), hypertension, increased cholesterol levels and increased blood sugar levels.

- Alopecia associated with the use of zafirlukast was reported in 4 patients. In one report the drug was discontinued in an 8-year-old girl because of hair loss, and montelukast (5 mg/d) was later initiated. Hair loss also occurred within 2 weeks after the start of the montelukast therapy, but it subsided within a month even though the montekulast was continued. In the other 3 cases (age range 35-47 years; 1 woman, 2 sex unknown), zafirlukast was discontinued because of hair loss.

- Fibromyalgia-like symptoms (joint inflammation, joint pain, back pain, pain in neck and shoulder) occurred in a woman within 3 days after initiating zafirlukast therapy and resolved with oral prednisone prescribed for asthma more than 2 months after zafirlukast was discontinued.

- A rash occurred in a man upon first and second trial of zafirlukast, and the following symptoms occurred 2 months after zafirlukast had been discontinued: myalgia, malaise, increase in erythrocyte sedimentation rate, abnormal liver function test results, increased blood creatinine level, increased serum iron level, photophobia and uveitis.

- Symptoms of fatty liver, increased hepatic enzyme levels, increased serum cholesterol level, hypertriglyceridemia, hyperlipemia and edema occurred in a man receiving montelukast therapy. Concomitant medications were Dyazide®, Becloforte® and salbutamol.

- Eye movements and head movements along with facial expression "freeze" diagnosed as a tic occurred 2-3 weeks after initiating montelukast 5 mg/d at bedtime in a 6-year-old girl. An electroencephalogram gave normal readings, and the only concomitant medication was ipratroprium (1000 µg/d via nebulizer) which had been initiated 2 weeks before montelukast therapy. The patient recovered without any treatment after montelukast was discontinued.

Other reports with unexpected adverse reactions had insufficient information to evaluate, but the CADRMP will continue to monitor.

At this time, the risk of adverse drug reactions is assumed to be shared across all leukotriene receptor antagonists because insufficient information is available to compare agents. Smith<9> stated that: "Initial experience with antileukotrienes reveals limited toxicity and what appears to be a favourable therapeutic-to-toxic ratio; however exposure of more patients with differing characteristics for longer periods of time is needed to substantiate this initial impression." As with any new class of drugs entering the market, adverse effects that occur at low frequency or in populations not studied in clinical trials may surface in the postmarketing period, and thus spontaneous reporting of unexpected or serious adverse effects is encouraged.

This article does not represent a review of all adverse drug reactions or drug–drug interactions reported in the literature or to the CADRMP. The product monographs should be consulted for labelled adverse drug reactions or interactions.

Written by: Marielle McMorran BSc (Pharm), Bureau of Drug Surveillance

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COMMUNIQUÉ

The purpose of this section is to increase awareness of ADRs recently reported to the CADRMP. The following cases have been selected on the basis of their seriousness, or the fact that the reactions do not appear in the product monograph. They are intended to prompt reporting. (The terminology used for expressing reactions is based on the World Health Organization's Adverse Reaction Dictionary using the "preferred term.")

Ropinirole (Requip™): sleep disorder

Sudden sleep attack associated with ropinirole use, a non-ergoline dopamine agonist indicated in the treatment of Parkinson's disease, was reported to the CADRMP.

If you have observed comparable cases or any other serious events, *please report them* to the Adverse Drug Reaction Reporting Unit, Continuing Assessment Division, Bureau of Drug Surveillance, AL 0201C2, Ottawa ON K1A 1B9; fax 613 957-0335; or to a participating regional ADR centre. The ADR form is available at:

www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/forms/adverse_e.pdf

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Please Note: A voluntary reporting system thrives on intuition, lateral thinking and openmindedness. For these reasons, most adverse drug reactions (ADRs) can be considered only to be suspicions, for which a proven causal association has not been established. Because there is gross underreporting of ADRs and because a definite causal association cannot be determined, this information cannot be used to estimate the incidence of adverse reactions. ADRs are nevertheless invaluable as a source of potential new and undocumented signals. For this reason, Health Canada does not assume liability for the accuracy or authenticity of the ADR information contained in the newsletter articles.

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